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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,737	11/06/2000	Stephen Quake	020174-001810US	8821

20350 7590 12/05/2001

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EXAMINER

CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
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1655

DATE MAILED: 12/05/2001

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/707,737

Applicant(s)

Quake

Examiner

Arun Chakrabarti

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Mar 8, 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6 20) ☐ Other:

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DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-40, drawn to method of analyzing nucleic acids by hybridization, classified in class 435, subclass 6.
 - II. Claims 41-54, drawn to apparatus for analyzing the sequence of polynucleotide, classified in class 435, subclass 288.
2. The inventions are distinct, each from the other because of the following reasons:

Inventions of Group I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP § 806.05(e)). In this case, the process of analyzing a target polynucleotide can be practiced by the apparatus of Group II or can be practiced by microchip array or by microtiter plates.
3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.
4. During a telephone conversation with Hugh Wang, on June 29, 2001, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-40.

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Affirmation of this election must be made by applicant in replying to this Office action. Claims 41-54 are withdrawn from further consideration by the examiner, 37 CAR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CAR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CAR 1.48(b) and by the fee required under 37 CAR 1.17(I).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 26 and 34 are rejected as indefinite because the instantly claimed methods lack a final process step that clearly relates back to the preamble. For the method of claims 1, 26 and 34, the preamble of the instantly claimed methods are drawn to a method for analyzing a target nucleic acid while the final process step is that of repeating steps (b)-(d) with a further nucleotide and it is thus unclear as to whether the instantly claimed methods are drawn to a method for

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analyzing a target nucleic acid or rather repeating steps (b)-(d) with a further nucleotide. Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claims 1, 26 and 34 lack such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

Claim 11 is rejected over the recitation of the phrase, "elastomeric materia". It is not clear if elastomeric materials are claimed or a novel and special type of fabrication is claimed. The metes and bounds of the claim is vague and indefinite.

Claims 37-40 are rejected over the recitation of the phrases, "fraction of the first nucleotide" and "fraction of the further nucleotide". It is not clear if some particular nucleotide parts of the entire nucleotides are claimed or ratio of the first and further nucleotides are claimed or both are claimed. The metes and bounds of the claims are vague and indefinite.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

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has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

9. Claims 1-7, 13, 15-21,, 26-28 and 34-36 are rejected under 35 U.S.C. 102 (e) as being anticipated by Livak et al. (U.S. Patent 5,945,284) (August 31, 1999).

Livak et al teach a method of analyzing a target polynucleotide (Abstract) comprising:

a) providing a primed target polynucleotide attached to a microfabricated synthesis channel (Abstract and Column 7, line 35 to column 8, line 12);

b) flowing a first nucleotide through the synthesis channel under conditions whereby the first nucleotide attaches to the primer, if a complementary nucleotide is present to serve as template in the target polynucleotide (Figure 2A-2C and Claim 1 and Column 10, lines 27-35);

c) determining presence or absence of a signal, the presence of a signal indicating that the first nucleotide was incorporated into the primer, and hence the identity of the complementary base that served as a template in the target polynucleotide (Figure 2A-2C and Claim 1 and Column 10, lines 27-35);

d) removing or reducing the signal, if present (Figure 2A-2C and Claim 1 and Column 10, lines 27-35); and

e) repeating steps (b)-(d) with a further nucleotide, the same or different from the first nucleotide, whereby the further nucleotide attaches to the primer or a nucleotide previously incorporated into the primer (Abstract, Column 10, lines 56-65 and Claim 1).

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Livak et al teach a method wherein step comprises providing a plurality of different primed target polynucleotides attached to each different synthesis channels (Column 2, lines 35-39);

Livak et al teach a method wherein the first nucleotide and further nucleotides are labeled (Column 8, line 44 to column 9, line 17 and Claim 6).

Livak et al teach a method wherein the steps (b)-(d) are performed until the identity of each base in the target polynucleotide has been identified (Abstract and Column 10, lines 56-65).

Livak et al teach a method wherein the removing or reducing is by photobleaching and by chemical release of the label (Column 13, lines 28-31 and Column 8, line 57 to Column 9, line 17).

Livak et al teach a method wherein the label is mass-spectrometric label (Column 8, lines 51-56).

Livak et al teach a method wherein at least one of the labeled nucleotide comprises a mixture of labeled and unlabeled forms of the nucleotide (Figures 2A-3B).

Livak et al teach a method of analyzing a target polynucleotide comprising:

- a) pretreating the surface of a substrate to create surface chemistry that facilitates polynucleotide attachment and sequence analysis (Column 7, line 35 to column 8, line 42);
- b) providing a primed target polynucleotide attached to the surface of a substrate (Figures 3A-3B);
- c) providing a labeled first nucleotides to the attached target polynucleotide under conditions whereby the labeled first nucleotide attaches to the primer, if a complementary

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nucleotide is present to serve as template in the target polynucleotide (Figures 3A-3B and Column 10, line 66 to Column 11, line 34);

d) determining presence or absence of a signal, the presence of a signal indicating that the labeled first nucleotide was incorporated into the primer, and hence the identity of the complementary base that serve as a template in the target polynucleotide (Figures 3A-3B and Column 10, line 66 to Column 11, line 34);

e) repeating steps c)-d) with a labeled further nucleotide, the same or different from the first labeled nucleotide, whereby the labeled further nucleotide attaches to the primer or a nucleotide previously incorporated into the primer (Figures 3A-3B and Column 10, line 66 to Column 11, line 34).

Livak et al teach a method wherein the label is a fluorescent label, radiolabel or non-optical signal (Column 12, lines 54-62 and Column 5, lines 43-54).

Livak et al teach a method wherein the substrate is glass and the surface is coated with a polyelectrolyte multilayer terminated with a polyanion (Column 8, lines 19-42).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-7, 13, 15-21, 26-28 and 34-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999).

Livak et al teach the method of claims 1-7, 13, 16-21, 26-28 and 34-36 as described above.

Livak et al do not teach the method wherein the fraction of the first nucleotide and the further nucleotide are less than 0.01%.

However, it is *prima facie* obvious that selection of the specific fraction of the first nucleotide and the further nucleotide represents routine optimization with regard to analyzing a target polynucleotide which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

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Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific fraction of the first nucleotide and the further nucleotide were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

12. Claims 1-11, 13-21, 26-28 and 34-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457).

Livak et al teach the method of claims 1-7, 13, 15-21, 26-28 and 34-40 as described above.

Livak et al do not teach the method wherein the synthesis channel is formed by bonding a microfluidic chip fabricated with an elastomeric material to a flat substrate.

Effenhauser et al. teach the method wherein the synthesis channel is formed by bonding a microfluidic chip fabricated with an elastomeric material to a flat substrate (Abstract and Figure 1 and Experimental Section).

Livak et al do not teach the method wherein the cross section of the synthesis channel has a linear dimension of less than 100 micrometer x 100 micrometer.

Effenhauser et al. teach the method wherein the cross section of the synthesis channel has a linear dimension of less than 100 micrometer x 100 micrometer (Figure 2 and Experimental Section, Fabrication of the Silicone Microchip Devices Subsection).

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It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the synthesis channel formed by bonding a microfluidic chip fabricated with an elastomeric material to a flat substrate of Effenhauser et al. into the method of Livak et al., since Effenhauser et al. state, "A simple and inexpensive molding procedure has been successfully demonstrated to allow for the fabrication of chip-based microfluidic devices. Relief structures on the silicone master are truly reproduced on the micrometer scale. The flat surfaces adhere without bonding procedures to a variety of smooth substrates, thus forming closed microchannel systems (Page 3457, Column 1, Conclusions Section, First three sentences)." Further motivation is provided by Effenhauser et al as Effenhauser et al state, "The combination of electrokinetic control of picoliter sample volumes and single-molecule detection can result in a novel tool for the manipulation of single molecular objects in solution, an emerging technology with far-reaching consequences in, for example, molecular diagnostics (Page 3457, Column 2, Conclusions Section, Last sentence)". By employing scientific reasoning, an ordinary artisan would have combined and substituted the flexible silicone microdevices of Effenhauser et al. into the method of Livak et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the synthesis channel formed by bonding a microfluidic chip fabricated with an elastomeric material to a flat substrate of Effenhauser et al. into the method of Livak et al. in order to achieve the express advantages , as noted by

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Effenhauser et al., of a novel tool for the manipulation of single molecular objects in solution, an emerging technology with far-reaching consequences in, for example, molecular diagnostics.

13. Claims 1-21, 26-28 and 34-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Koster (U.S. Patent 6,225,567 B1) (May 1, 2001).

Livak et al in view of Effenhauser et al. teach the method of claims 1-11, 13-21, 26-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al do not teach the method wherein the elastomeric material is RTV silicone.

Kester teaches the method wherein the elastomeric material is RTV silicone (Column 7, line 63 to column 8, line 11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the elastomeric material RTV silicone of Kester into the method of Livak et al. in view of Effenhauser et al, since Kester states, "Performance is improved because the elastomeric housing can conform to irregularities in the array, particularly if it is used in conjunction with a silane surface treatment and/or a silicone RTV material (Column 8, lines 63-66)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the silicone RTV material of Kester into the method of Livak et al. in view of Effenhauser et al in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the

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elastomeric material RTV silicone of Kester into the method of Livak et al. in view of Effenhauser et al. in order to achieve the express advantages, as noted by Kester, of a novel silicone material that provides improved performance because the elastomeric housing can conform to irregularities in the array.

14. Claims 1-11, 13-22, 24-28 and 34-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Williams (U.S. Patent 6,232,075 B1) (May 15, 2001).

Livak et al in view of Effenhauser et al. teach the method of claims 1-11, 13-21, 26-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al do not teach the method wherein the pyrophosphate release is detected with an enzymatic reaction.

Williams teaches the method wherein the pyrophosphate release is detected with an enzymatic reaction.(Figure 1B and Column 5, line 55 to column 6, line 22).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the pyrophosphate release detection with an enzymatic reaction of Williams in the method of Livak et al in view of Effenhauser et al, since Williams states, "The present invention provides a heterogeneous assay for the detection of pyrophosphate. The detection of pyrophosphate is advantageous in a number of biological reactions (Column 5, lines 55-58)." By employing scientific reasoning, an ordinary artisan would

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have combined and substituted the pyrophosphate release detection with an enzymatic reaction of Williams in the method of Livak et al in view of Effenhauser et al in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the pyrophosphate release detection with an enzymatic reaction of Williams in the method of Livak et al in view of Effenhauser et al in order to achieve the express advantages, as noted by Williams, of an invention that provides a heterogeneous assay for the detection of pyrophosphate advantageous in a number of biological reactions.

15. Claims 1-11, 13-28 and 34-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Williams (U.S. Patent 6,232,075 B1) (May 15, 2001) further in view of Koster (U.S. Patent 6,140,053) (October 31, 2000).

Livak et al in view of Effenhauser et al. further in view of Williams teach the method of claims 1-11, 13-22, 24-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al further in view of Williams do not teach the method wherein the pyrophosphate release is detected with mass spectrometry.

Koster teaches the method wherein pyrophosphate release is detected with mass spectrometry (Figure 10 and Column 10 , lines 30-48).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the mass spectrometry of Koster into the method of Livak et al. in view of Effenhauser et al further in view of Williams, since Kester

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states, "The invention provides fast and highly accurate mass spectrometer based process for directly sequencing a target nucleic acid (Abstract)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the mass spectrometry method of Kester into the method of Livak et al. in view of Effenhauser et al further in view of Williams in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the mass spectrometry of Koster into the method of Livak et al. in view of Effenhauser et al further in view of Williams in order to achieve the express advantages, as noted by Koster, of an invention that provides fast and highly accurate mass spectrometer based process for directly sequencing a target nucleic acid.

16. Claims 1-11, 13-21, 26-29 and 34-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Clark et al. (U.S. Patent 6,242,528 B1) (June 5, 2001).

Livak et al in view of Effenhauser et al. teach the method of claims 1-11, 13-21, 26-28 and 34-40 as described above.

Livak et al in view of Effenhauser et al do not teach the method wherein the polyanion bears pendant carboxylic acid groups.

Clark et al. teach the method wherein the polyanion bears pendant carboxylic acid groups (Column 3, lines 32-50).

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It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the pendant carboxylic acid groups containing polyanions of Clark et al. into the method of Livak et al. in view of Effenhauser et al, since Clark et al. state, "Such acrylic-modified waterborne alkyds are useful in a variety of coating compositions (Abstract, last sentence)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the pendant carboxylic acid groups containing polyanions of Clark et al. into the method of Livak et al. in view of Effenhauser et al in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the pendant carboxylic acid groups containing polyanions of Clark et al. into the method of Livak et al. in view of Effenhauser et al. in order to achieve the express advantages, as noted by Clark et al., of a novel waterborne alkyds containing pendant carboxylic acid groups useful in a variety of coating compositions.

17. Claims 1-11, 13-21, 26-32 and 34-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Clark et al. (U.S. Patent 6,242,528 B1) (June 5, 2001) further in view of Batz et al. (U.S. Patent 6,225,052 B1) (May 1, 2001).

Livak et al in view of Effenhauser et al. further in view of Clark et al. teach the methods of claims 1-11, 13-21, 26-29 and 34-40 as described above.

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Livak et al in view of Effenhauser et al. further in view of Clark et al do not teach the target polynucleotide is biotinylated and surface is coated with biotin and streptavidin.

Batz et al teach the target polynucleotide is biotinylated and surface is coated with biotin and streptavidin (Figure 4 and Column 23, lines 38-52).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the biotinylated target polynucleotide and surface coated with biotin and streptavidin of Batz et al into the method of Livak et al. in view of Effenhauser et al further in view of Clark et al., since Batz et al state, "The assay format using an immobilized probe is especially advantageous if the sample contains further ingredients disturbing the irradiation of a detection, for example, by absorbing light in the range of the irradiation or emission wavelength (Column 23, lines 48-52)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the biotinylated target polynucleotide and surface coated with biotin and streptavidin of Batz et al into the method of Livak et al. in view of Effenhauser et al further in view of Clark et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the biotinylated target polynucleotide and surface coated with biotin and streptavidin of Batz et al into the method of Livak et al. in view of Effenhauser et al further in view of Clark et al in order to achieve the express advantages, as noted by Batz et al, of an assay format using an immobilized probe which is especially advantageous if the sample contains

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further ingredients disturbing the irradiation of a detection, for example, by absorbing light in the range of the irradiation or emission wavelength.

18. Claims 1-11, 13-21, 26-28, and 30-40 are rejected under 35 U.S.C. 103 (a) over Livak et al. (U.S. Patent 5,945,284) (August 31, 1999) in view of Effenhauser et al. (Analytical Chemistry, (1997), Vol. 69, pages 3451-3457) further in view of Clark et al. (U.S. Patent 6,242,528 B1) (June 5, 2001) further in view of Batz et al. (U.S. Patent 6,225,052 B1) (May 1, 2001) further in view of Liu (U.S. Patent 6,165,694) (December 26, 2000).

Livak et al in view of Effenhauser et al. further in view of Clark et al. further in view of Batz et al. teach the method of claims 1-11, 13-21, 26-28, 30-32 and 34-40 as described above.

Livak et al in view of Effenhauser et al. further in view of Clark et al. further in view of Batz et al do not teach the method wherein the surface is pretreated with RCA solution.

Liu teach the method wherein the surface is pretreated with RCA solution.(Column 2, lines 52-53 and Column 3, lines 46-65)

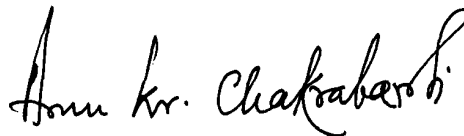
It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the pretreatment with RCA solution of Liu into the method of Livak et al. in view of Effenhauser et al further in view of Clark et al. further in view of Batz et al., since Liu states, "Subsequently, an RCA solution is used to clean the surfaces to remove unwanted impurities (Column 2, lines 52-53)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the RCA solution of Liu into the method of Livak et al. in view of Effenhauser et al further in view of Clark et al. further in

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view of Batz et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the pretreatment with RCA solution of Liu into the method of Livak et al. in view of Effenhauser et al further in view of Clark et al. further in view of Batz et al. in order to achieve the express advantages, as noted by Liu, of an RCA solution which is used to clean the surfaces to remove unwanted impurities.

Conclusion

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

A handwritten signature in cursive script, reading "Arun Chakrabarti".

Arun Chakrabarti,

Patent Examiner,

December 4, 2001